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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/21/2005

Kurt Eyer

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EXAMINER

HANLEY, SUSAN MARIE

ART UNIT

PAPER NUMBER

1651

MAIL DATE

DELIVERY MODE

12/11/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/553,911	Applicant(s) EYER ET AL.	
	Examiner SUSAN HANLEY	Art Unit 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 September 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment and reply filed 9/2/08 are acknowledged.

Claims 1-22 are under examination.

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-22 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Omura et al. (US 4,107,297; cited in the IDS filed 1/4/08) in view of Hershberger et al. (US 4,637,981), Borghi et al. (US 5,135,857) and Nabais (1995).

Applicant argues that the Examiner has incorrectly attempted to generify the limited disclosure of Omura et al. and that Omura does not a discloses the recovery of staurosporine from a fermentation broth. Applicant argues that Omura does not teach an ultrafiltration step. Applicant argues that Omura teaches away from diafiltration because Omura discloses that staurosporine is fat soluble and that the loss of product from ethyl acetate results in the loss of some staurosporine. Applicant asserts that "Omura would teaches extraction of AM-2282 with sparingly soluble in butyl acetate and one of ordinarily skilled in the art would be directed away from the use of Omura et al. in the search for the claimed invention."

Applicant argues that Omura extracts AM-2282 from water using ethyl acetate, which directs away from applicants' use of a mixture of water and ethyl acetate (or other organic solvent B)) to extract from the retentate of the diafiltration, thus showing the unobviousness of Claims 6, 11 to 13 and 18. Applicant argues that the disclosure by

Omura of evaporation, chromatography on silica gel and recrystallization does not make instant claim 10 obvious as a whole.

Applicant asserts that the statement by Omura that staurosporine recovery can be achieved by "known methods for separating antibiotics" is so broad as to be meaningless under Section 103(a) and clearly would cover many of such process that would be inoperable for AM-2282 and applicants' claimed process.

Applicant argues that the rejection of claims 2 to 11, 13, 14 and 18 because they limit steps that are indicated as optional in Claim 1 has no basis in law and that the Examiner and he has not cited any support in law for his position. Applicant concludes that said claims are allowable. Applicant asserts that the term "optionally" means that there are two processes - one without the optional step included and one with the optional step included. Applicant cites M.P.E.P., 2173.05(h)(111), which states "...was considered acceptable alternative language because there was no ambiguity as to which alternatives were covered by the claim." Applicant asserts that the Examiner has not shown that any such ambiguity is present.

Applicant asserts that the statement regarding what Omura does not teach is an admission of nonobviousness. Applicant argues that the Examiner has not shown why one ordinarily skilled in the art would combine the three secondary rejection references with Omura et al. in the search for applicants' claimed invention.

Applicant argues that Hershberger directs one ordinarily skilled in the art away from applicants' claimed invention because Hershberger does not teach a basic pH which is required by the instant application. Applicant asserts that all of the teachings of

a reference and the prior art of record must be considered under Section 103(a) and that when the teachings of the rejection references are in direct conflict and there is no basis for choosing one conflicting teaching over the other, there is no basis for a holding of obviousness. Applicant argues that filtration with diatomaceous earth or other commercially available filter aids does not make the claimed invention obvious.

Applicant argues that Hershberger teaches centrifugation, evaporation and Hershberger's teaching that factor G can be isolated by conventional isolation features do not make the invention obvious. Applicant argues that the examiner has not demonstrated why the ordinary artisan would combine Hershberger with the other references. Applicant argues that the disclosure by Nabais and Borghi make broad statements that do not make applicants' invention as a whole obvious. Applicant argues that the assertion that Borghi establishes that methods for the recovery of antibiotics from biological sources are well established in the art is a broad statement that is meaningless.

Applicant argues that the Examiner has not determined in the record the level of ordinary skill in the art, without which a valid obviousness rejection can be made. Applicant argues that the Examiner's use of the term "ordinary artisan" is meaningless under Section 103(a) because it is not the same as "the artisan ordinarily skilled in the art" ("one ordinarily skilled in the art") which is the standard required under Section 103(a). Wherever the Examiner has used such term, the statement is meaningless under Section 103(a). Applicant argues that the citation of *Ex parte Kubin*, 83 USPQ2d 1410 (Bd. Pat. App. & Int., 2007), is not relevant because it only deals with the situation

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where the level of ordinary skill in the art has already been determined. Applicant argues that the cited Board decision is not relevant to this case because it does not deal with the determination of the level of ordinary skill in the art but only deals with one ordinarily skilled in the art. (Applicant asserts that the Patent Office and Supreme Court requires determination of the level of ordinary skill in the art as a mandatory prerequisite before a valid decision of obviousness can be made under Section 103(a). The Applicant asserts that all statements regarding the references, the combination of references and what a reasonable expectation is are meaningless under Section 103(a) because it is based upon "the ordinary artisan" and the Examiner does not know what would be a reasonable expectation to one ordinarily skilled in the art.

Applicant argues that the claimed invention which teaches the addition of a water-miscible organic solvent such as methanol, ethanol, propanol, 2-propanol, tert-butanol, acetone or tetrahydrofuran and the adjustment to a pH of at least 8.5 in a method to purify staurosporine - is not obvious in view of the "(attempted) combination of references" cited by the Examiner. Omura et al. teaches the use of n-butyl acetate which is only slightly soluble in water (0.7% at 20 °C) and not the use of a water-miscible organic solvent. Although Omura et al. states that staurosporine is only sparingly soluble in butyl acetate, there is no suggestion or motivation by Omura et al. to search for an alternative way of extracting staurosporine. Further, even though Hershberger et al. teaches the use of a water miscible organic solvent such as acetone for the isolation of an antibiotic, it should be noted that staurosporine and factor G, i.e., the antibiotic of Hershberger et al., are different molecules having different solubility in

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different solvents. Applicant question whether a method which functions to isolate one antibiotic is also applicable for the isolation of a different antibiotic. Applicant points out that Hershberger et al. does not describe the use of a water miscible organic solvent alone, but instead teaches a combination of using a water miscible organic solvent such as acetone and subsequently the acidification of the whole diluted fermentation broth. Applicant concludes that Hershberger. teaches away from the instantly claimed invention which claims adjustment to a pH of at least 8.5. Applicant asserts that a multi-step process for the isolation of staurosporine is claimed and that a prior art document which describes only one step of such multi-step process does not make the claimed invention multi-step process obvious to one ordinarily skilled in the art. Applicant argues that the attempted combination of rejection references directs away from applicants' claimed invention.

Responding to applicant's argument regarding the generification of Omura, that Omura does not teach the isolation of staurosporine from a fermentation broth, the claims and specification (see the examples) in the Omura patent are drawn to the fermentation and recovery of staurosporine. Responding to Applicant's assertion that Omura teaches away from diafiltration due to loss of product, a 100% recovery of product from any purification is extremely rare and it is unclear why an expected loss of product during isolation teaches away from diafiltration. Previously, the rejected claims did not recite a diafiltration step due to the alternative language ("optionally") the diafiltration steps was not considered since one has the choice of executing the step. The claims were rejected based on the alternative that the diafiltration step is not

performed. New claims 19-22 require ultrafiltration and diafiltration. Nabais disclose that ultrafiltration in combination with diafiltration of fermented broths containing antibiotics (note the generification for all antibiotics) using FP10 membrane is a valid alternative to the use of rotary vacuum filters, flocculants and filter aids (abstract). Hence the ordinary artisan would have been motivated to modify the combined disclosures of Omura, Hershberger and Nabais and to employ ultrafiltration in combination with diafiltration to obtain staurosporine from a fermented broth because the method is superior to older methods of filtration of product. The ordinary artisan would have had a reasonable expectation of success because Nabais discloses the success for obtaining clavulanic acid using the combined method (see Table 6)..

Regarding Applicant's assertion that staurosporine was sparingly soluble in butyl acetate and teaches away from the invention, Omura specifically teaches that the extraction can be performed with an "suitable solvent" (col. 6, lines 55-57). This is a clear indication that the ordinary artisan that Omura expects that the ordinary artisan can select an extraction solvent. Furthermore, the ordinary artisan would have been motivated to employ a miscible solvent given the low solubility in water and butyl acetate.

Responding to Applicant's argument that Omura's extraction of staurosporine with ethyl acetate teaches away from claims 6, 11-13 and 18, the claims were rejected because they limit steps that are indicated as optional in claim 1. For the purposes of this rejection, the claims were interpreted that the optional steps are not performed. Responding to Application argument that Omura's disclosure of evaporation, etc. and

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the motivational statement that clearly teaches the purification of staurosporine can be purified by known methods do not make instant claim obvious as a whole, the argument is non-persuasive because that are allegations without factual support.

Responding to Applicant's assertion that there is no basis in the law for not examining claims 2-11, 13, 14 and 18, this argument is not persuasive because it is clear that the dependent claims can depend from the option of diafiltering, which is clearly indicated as optional. The dependent claims do not specifically marry the dependent limitations to one alternative (performing step iii) or not performing step (iii). The examiner concurs with Applicant's meaning of "optionally" because it clearly defines "optionally" "that there are two processes - one without the optional step included and one with the optional step included." Hence, "optionally" indicates that the optional steps are in the alternative (e.g., they are performed or they are not performed). The examiner agrees that ambiguity has not been shown because the alternative language implied by "optional" is clear.

Applicant's assertion with respect to what Omura does not teach is not an admission of nonobviousness. It is a well known standard for the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applicant assertion that the examiner has not demonstrated the motivation for the combination of references is, again, an allegation without factual support and, therefore, non-persuasive.

Responding to Applicant's arguments that Hershberger does not teach a basic pH, that Hershberger's use of conventional isolation procedures and the examiner's has not demonstrated a motivation to combine Hershberger with the other references, the arguments are non-persuasive because they are allegations without factual support (e.g., in what way has the examiner failed to show a lack of motivation to combine references when such statements are made in the rejection?)

Responding to Applicant's assertion that Nabais and Borghi make broad statements that do not make applicants' invention as a whole obvious, this argument is non-persuasive because it is an allegation without factual support, and therefore, non-persuasive.

Responding to Applicant's assertion that the term "ordinary artisan" is meaningless and not the same as the "artisan ordinarily skilled in the art," any practitioner in the field of patents would recognize that the phrase "ordinary artisan" is a synonym for "artisan ordinarily skilled in the art". Applicant is directed, for example, directed to MPEP page 2100-12 under section c): "requires a determination of the level of skill of the ordinary artisan" or MPEP 2143, part g:

The Courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Id.* at 1366, 80 USPQ2d at 1649. "[A]n implicit motivation to combine exists not only when a suggestion may be gleaned from the prior art as a whole, but when the 'improvement' is technology-independent and the combination of references results in a product or process that

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is more desirable, for example because it is stronger, cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient. Because the desire to enhance commercial opportunities by improving a product or process is universal-and even common-sensical-we have held that there exists in these situations a motivation to combine prior art references even absent any hint of suggestion in the references themselves. In such situations, the proper question is whether the ordinary artisan possesses knowledge and skills rendering him capable of combining the prior art references." *Id.* at 1368, 80 USPQ2d at 1651 (emphasis added).

Responding to Applicant's arguments that because the term "ordinary artisan" is meaningless, the citation of *Ex parte Kubin*, is not relevant the level of one ordinarily skilled in the art has not been determined, as required by Patent Office and the Supreme Court, Applicant is invited to peruse MPRP 2143.03, Part II:

II.< SPECIFYING A PARTICULAR LEVEL OF SKILL IS NOT NECESSARY WHERE THE PRIOR ART ITSELF REFLECTS AN APPROPRIATE LEVEL

If the only facts of record pertaining to the level of skill in the art are found within the prior art of record, the court has held that an invention may be held to have been obvious without a specific finding of a particular level of skill where the prior art itself reflects an appropriate level. *Chore-Time Equipment, Inc. v. Cumberland Corp.*, 713 F.2d 774, 218 USPQ 673 (Fed. Cir. 1983). See also *Okajima v. Bourdeau*, 261 F.3d 1350, 1355, 59 USPQ2d 1795, 1797 (Fed. Cir. 2001).

>

In the instant case, Omura, Hershberger and Borghi issued in 1978, 1987 and 1992, respectively. The dates of these documents, one of which is 30 years old, clearly establish that the ordinary artisan of the present day would be fully knowledgeable of antibiotic isolation procedures from a fermentate including extraction, concentration, filtration methods, etc.

Responding to Applicant's argument Omura teaches away from water-miscible organic solvents, Omura clearly state that the ordinary artisan can use a "suitable solvent" (col. 6, lines 55-57). It is well within the skill of the ordinary artisan to select extraction solvents. Hershberger provides examples of such solvents that are suitable for antibiotic extraction from a broth. Regarding Applicant's argument that the pH range

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taught by Hershberger teaches away from using a pH of greater than 8.5 for staurosporine isolation, said limitation was taught by Omura. Regarding Applicant's argument that it is improper to make a multi-reference rejection for a multi-step process based on a single reference that teaches only one step, antibiotic isolation is an art having well known techniques. Omura specifically teaches that staurosporine recovery can be achieved by "known methods for separating antibiotics" (col. 6, lines 41-42). Thus, the isolation of staurosporine by the claimed method is obvious in the absence of unexpected results.

Regarding the references that were submitted with the response filed 9/2/08, Applicant is invited to specifically point out how each reference supports his/her position.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN HANLEY whose telephone number is (571)272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sandra Saucier/
Primary Examiner, Art Unit 1651

/Susan Hanley/
Examiner, Art Unit 1651

